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Sequential Analyses of Daily Symptoms in Women With Fibromyalgia Syndrome

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Abstract: Fibromyalgia syndrome (FMS) is a chronic musculoskeletal pain disorder characterized by generalized pain, chronic fatigue, sleep disturbance, and a range of other symptoms having no definitive pathology. Consequently, patient evaluations rely on self-report. Ecological Momentary Assessment (EMA) allows frequent real-time collection of self-report measures, removing recall bias and increasing external validity. We studied 81 females with FMS aged 18 to 42 years. Participants carried EMA devices (Palm Pilot M100) programmed to request ratings to 8 FMS symptoms/conditions 3 times daily for 30 days. Completeness of response rates varied across participants and over time. Controlling for immediately previous fatigue (ie, fatigue rating from the immediately preceding rating), unit increases in immediately previous pain and immediately previous emotional distress predicted 9 and 7% increases, respectively, in current fatigue. Controlling for immediately previous emotional distress, a unit increase in immediately previous pain predicted 7% increase in current emotional distress. Controlled for immediately previous pain, a unit increase in immediately previous fatigue predicted a 7% increase in current pain, enhanced by prior diurnal effects; immediately previous emotional distress was not significant. Collectively these results suggest an asymmetry in which emotional stress and pain may increase fatigue, fatigue but not emotional distress may increase pain, and pain but not fatigue may increase emotional distress. Despite small effects and person-to-person variability, these findings suggest that longitudinal data collection by EMA may reveal sequential or causal explanatory patterns with important clinical implications.

***Perspective:** Understanding how multiple symptoms covary in FMS is essential for optimal treatment planning. Our results show that small but significant temporal relations among pain, fatigue, and emotional distress. Our results also provide support for the use of EMA as a viable data collection method that allows longitudinal, real-time assessment of multiple FMS symptoms.*

***Key words:** Fibromyalgia, Ecological Momentary Assessment, pain, fatigue, mood, sequential analyses.*

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal pain disorder characterized by generalized pain, chronic fatigue, sleep disturbance, and a range of other symptoms.[44] The current classification depends upon self-report of chronic diffuse pain (all 4 quadrants of the body and along the axial skeleton) of at least 3 months' duration and positive pain response to at least 11 of 18 designated tender points (TPs).[44] The etiology of FMS is unknown and there is no objective pathology associated with FMS, yet FMS is a disabling disorder that adversely affects quality of life in those afflicted.[6]

In the absence of definitive pathology, the critical aspect for evaluating FMS patients relies upon patients to report the presence and degree of symptoms. Typical assessment involves asking patients what their levels of symptom severity have been over some period of time (eg, week or month). This process requires the patient to recall the occurrence, nature, and magnitude of their symptoms and then to aggregate and average this information to arrive at a summary rating.

Although we commonly rely on patient's recall to assess their symptoms, the validity and accuracy of the retrospective assessment method has been questioned. Inaccurate recall of pain severity in chronic pain has been frequently reported.[4,8,10,21,37] Recalled pain levels are influenced by a host of related factors such as pain level at the time of recall,[10] emotional distress,[18] and

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beliefs about their conditions.[25] These results all point to the importance of prospective assessment, preferably occurring in real-time, and using multiple sampling strategies to assure an adequate level of external validity.[34] Ecological Momentary Assessment (EMA) is a methodology that makes use of sample strategies that assess phenomena as they occur in natural settings by using a hand-held computer. This approach has the advantage of avoiding retrospective recall bias.

Furthermore, longitudinal assessment of multiple symptoms provides an opportunity to evaluate interrelationships between symptoms across time. This approach permits identification of symptoms, sleep quality, and activities that may exacerbate FMS patients' conditions. As a multisymptom disorder, how various symptoms associated with FMS relate over time to one another is of particular interest. For example, over 65% of FMS patients report that poor sleep and stress tend to exacerbate their FMS symptoms.[27] Results from time-series analyses[16] have provided some preliminary support for the sequential relationship between the psychosocial factors and pain. In the current study, we used EMA-collected symptom data to determine the relationships among FMS symptoms (pain, fatigue, and distressed mood) over time.

Significant cross-sectional relationships between negative mood and pain[17,33] and perceptions of fatigue[26] in FMS have been reported. However, the implication of these cross-sectional results is limited to correlational occurrences of these symptoms. Longitudinal, time-lagged analyses are needed for better understanding of changes in a symptom as a function of changes in other symptoms. EMA has been used in studies with other chronic pain populations, yielding significant time-lagged relationships between mood and pain in rheumatoid arthritis[1] and complex regional pain syndrome patients.[12]

The present study was conducted to extend understanding of the temporal covariations among pain, fatigue, and emotional distress in people with FMS on a longitudinal basis over a period of 30 days using the EMA method. We expected to see reciprocal temporal relationships among those variables, reflecting the complexity of this multisymptom pain disorder. As this was a fairly long assessment period, with EMA prompts occurring 3 times a day, we were also interested in examining adherence and how the long assessment period may have impacted the prevalence of missing data.

Methods

The research protocol was approved by the Institute Review Board at the University of Utah. All participants provided written consent prior to their entering the study.

Participants

The sample included 81 women with FMS. Because this was a part of a larger study evaluating the effect of naturally occurring hormonal fluctuation on FMS, all participants were regularly menstruating and not taking hormonally based contraception. The upper age limit was set at 42 to minimize the probability of unpredictable hormonal events related to peri-menopause, since the average age onset of peri-menopausal phase is approximately 45.[42] The participants were recruited from the Pain Management Center at the University of Utah Health Science Center, community rheumatologists and physicians, and via advertisement on campus and community. During the phone screening, they confirmed that they have been diagnosed with FMS by their physicians. During their first visit, in order to confirm the FMS classification by the American College of Rheumatology (ACR) criteria,[44] all participants underwent a standardized TP examination and completed a pain diagram to indicate the locations of pain (described below). The exclusion criteria include the use of opioids, clinical dose of tricyclics (eg, 75 mg amitryptline or equivalent), benzodiazepine, beta blockers, calcium channel blockers, vasodilator, nitrates, and digitalis; resting diastolic BP >115 mm Hg, systolic BP >200 mm Hg; known serious psychopathology (eg, psychosis, organic mental disorder); other comorbid pain disorder (eg, rheumatoid arthritis, painful diabetic neuropathy); and serious progressive medical condition (eg, cancer, Parkinson's disease). Additionally, participants were excluded if they met the diagnostic American Psychiatric Association (DSM-IV-TR) criteria for Premenstrual Dysphoric Disorder.[2]

The mean age of the sample was 28.75 (SD = 6.24), with the mean pain duration of 220.64 months (SD = 178.05, Median = 177 months). Their demographic background and pain history are listed in Table 1.

Apparatus

Palm Pilot M100s (Palm Inc., Sunnyvale, CA) were used for the EMA. Each Palm Pilot was custom programmed (TikiSoft, Orange, CA) to disable all the functions except for the EMA questions and prompting intervals. The device was generally kept at the standby mode. For each participant, 3 time intervals were programmed: Morning (from the time of waking to 11:59 AM), early afternoon (noon to 4:59 PM), and late afternoon (5:00 PM to 8:59 PM). The device was programmed to emit audible tones to indicate the EMA request once in each of the 3 time slots. We will refer to each of these time intervals as an "epoch" throughout this paper. Thus, there are 3 assessment epochs a day. The exact timing of the request was randomly varied within a time interval.

Procedures

Standardized TP Examination

During the initial visit, all study participants underwent a TP examination using the standard protocol: Manual Tender Point Survey.[29] A research nurse, trained by a physician specialized in pain medicine, palpated 18 (9 bilateral) ACR-determined TPs and 3 control points (ie, the midforehead, left thumb, and midright forearm) in a predetermined order using the thumb of the

Table 1. Demographic Background and Pain History of the Sample (n = 81)

Age	28.75 (6.24)
Race (white)	89%
Married	49%
Education (> college)	37%
Employed	54%
Height (inches)	64.27 (2.56)
Weight (pounds)	162.69 (40.93)
Pain duration (months)	220.64 (178.05)
Pain onset	
Accident/injury	11%
Following illness	16%
Insidious	48%
Current medication	
NSAIDs	47%
Tricyclics	9%
SSRIs/SNRIs	27%
Muscle relaxant	9%

dominant hand applying 4 kg of force at the rate of 1 kg/second. Following each palpation, participants indicated whether the palpation was painful, and rated the degree of painfulness on a scale of 0 to 10 (0 = no pain, 10 = worst pain). All patients met the ACR TP criterion[44] (at least 11/18 positive TPs) for the classification of FMS.

Widespread Pain

In order to assess whether participants met the widespread pain criterion of FMS classification, we asked participants to indicate the location of their pain on the Pain Drawing.[24] The Pain Drawing consists of the dorsal and ventral outline of a human figure with the body divided into numbered regions.

EMA

Each participant was asked to carry a Palm Pilot (Palm Inc.) at all times during waking hours for 30 consecutive days. A day was divided into 3 epochs, and there was 1 prompt in each of the first epoch (time participant wakes up to 11:59 AM), second epoch (noon to 4:59 PM), and third epoch (5:00 PM to 8:59 PM). Each signaling prompt was randomized within an epoch. Participants were asked to use an alarm clock programmed into the Palm Pilot to indicate when they are sleeping. For each signaling prompt, an audible tone signaled a data entry request. The tone signal lasted 60 seconds. If not answered within this time, the tone would be repeated 5 minutes later, and if not answered again, 5 minutes later. Failure to answer this sequence of 3 requests for data entry produced a missing entry for that epoch. If the prompt occurred at an inconvenient moment, participants were able to delay the assessment for up to 20 minutes. Because data entry requests were signaled randomly and participants were unable to predict the exact timing of the signal, the allowance of 20 minute delay appeared reasonable to minimize the intrusiveness of the EMA. Since the EMA was a random sampling procedure, this delay likely would not undermine the quality of the EMA data.

EMA questions were presented 1 at a time in a fixed order on a liquid crystal display. Participants were asked to respond to each question by scrolling across fixed response options with backward and forward arrows and then pressing an enter button to save the response and its time stamp on an Electronically Erasable Programmable Read-Only Memory data pack. Within an epoch, the responders could move backward to change their response to a prior question; however, once they completed the responses for that assessment epoch and saved them, participants could not access the data, nor could they access data from prior assessment epochs.

At each EMA epoch, participants were asked to rate their present levels for 8 symptoms or conditions: overall pain, fatigue, head pain, emotional distress, abdominal pain, sense of relaxation (reverse of stress), muscle pain, and sense of swelling. We used 3 items: overall pain, fatigue, and emotional distress given our primary interest in this study. Participants were to provide ratings using a 7-point scale, where 0 indicated "not at all" and 6 indicated "extremely." During the morning epoch, 2 additional sleep-related questions were asked. A sample display screen shot is shown in Fig 1.

Participants were asked to return to the laboratory at the end of the 30-day trial period and return their Palm Pilots. The Research Associate then uploaded data from the Palm Pilots to a desktop computer via a serial link. Data were automatically entered into a spreadsheet file for subsequent analysis.

Analysis of Sequential Relationships Among Pain, Fatigue, and Emotional Distress

Although the study included 8 EMA variables, we have decided to use 3 variables to evaluate the sequential relationship. We selected pain, fatigue, and emotional distress because we considered these as main FMS-related problems and we wanted to contain the number of variables to keep the interpretations of the analyses parsimoniously directional. To assess the sequential effects among these variables, we conducted a series of mixed-effects analyses that examined sets of lagged regressions allowing the coefficients to differ across individuals (the random effects) about overall population average coefficients (the fixed effects). For each symptom measure X, we identified 1 outcome, "current X", representing the current value of X. Then we constructed 1 variable, "prior X", representing the observation on measure X obtained for the immediately preceding epoch ("current X–1 Epoch"), and a second variable, "yesterday's X",

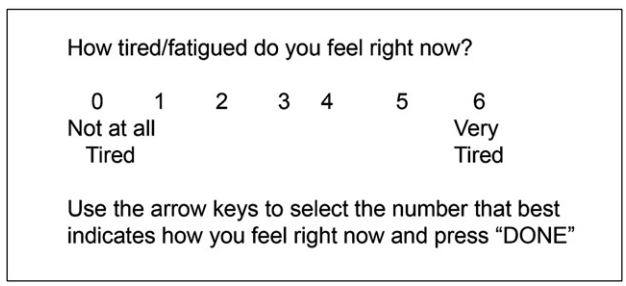

Figure 1. Sample EMA screen.

representing the observation on measure X made during the same epoch on the previous day ("current X–1 Day"). We decided to examine values obtained at about the same time on the previous day in order to identify any potential time-of-day factors. Thus, each of the 3 outcome variables (current pain, fatigue, and emotional distress) received potential contributions from 6 predictor variables (prior and yesterday's values for each of the 3 symptoms), collectively designated the "relevant past" of current measurements. This allowed us to inspect statistically controlled sequential relationships between symptom variables by modeling the associations between each outcome variable and combinations of the 6 predictor variables composing the relevant past.

Applying a backward stepwise procedure, we first tested a model for each variable of interest (pain, fatigue, and emotional distress) with all predictor variables from the relevant past entered as fixed and random effects, eliminating the variable having the highest *P* value for the random effects, then testing the model using the remaining predictors, continuing in this fashion until all remaining random effects terms were significant. We then constructed a similar procedure, removing fixed effects in turn until all remaining fixed effects coefficients were significant. The models included repeated measures for day and epoch, applying a variance components model for the fixed and random effects covariance structure and scaled identity for the repeated values conditional on the random effects. Finally, we compared the resulting model with the same model parameters when applying an unstructured random effects model. We then selected the model having the lowest Bayesian Information Criterion (BIC),[31] as it generally indicates the best fitting parsimonious model.

Since all of the models examined included current observations (the outcome variable of interest) and past observations (predictor variables) on all symptom measures, the models can be interpreted as providing a control for the relevant past of the outcome variable. The concept of a "Granger cause"[11,15] applies here. Predictor variable A is said to "Granger-cause" outcome variable B if a past value of A contributes to the prediction of B above and beyond the contribution made by past values of B and other predictors from the relevant past. Therefore, any predictor variable that significantly predicts an outcome variable, when that outcome variable is controlled for by its relevant past, can be interpreted as a possible cause of the outcome. When this condition applies, it is referred to as a "Granger cause." Applying this reasoning, we inspected the results of the models for asymmetries in the associations between predictor variables and outcome variables in an effort to identify possible causal (Granger-causal) relationships.

Results

Tender Points

Positive TPs ranged from 12 to 18, with a mean number of 16.65 (1.67) and a mean pain severity score of 4.15 (SD = 1.63).

EMA Response Rates

There were a total of 7,290 possible assessment epochs (3 epochs a day × 30 days × 81 participants). There were 6 participants who carried the Palm Pilot for less than 30 days (all had >20 days) due to logistical reasons and 11 epochs did not register due to technical problem. Thus, there were a total of 7,147 possible assessment epochs, and of these, 5,734 responses were entered, resulting in an 80.2% response rate. Participant response rates varied from 17 to 99%. The majority of patients (67%) had fewer than 20% of missing rates, and half of these patients had fewer than 10% missing responses. When we look at the time line, during the first week, the overall missing rate was 13.64%; it increased to 19.90% during the second week and to 22.90% during the final assessment week. The difference was statistically significant ($\chi^2(3) = 57.72$, $P < .001$). Fig 2 shows the daily percentages of missing responses across 30 days.

In order to examine whether certain demographic or FMS-related parameters were associated with poor response rates, patients were divided in 2 groups according to missing rate. We took a 30% missing rate as a significant degree of missingness; those having more than 30% missing responses (n = 17), and those having 30% or fewer missing responses (n = 64). The 2 groups did not differ significantly in age, marital status, educational level, or racial status. Pain duration and onset were also comparable between groups. Mean TP counts, TP intensity scores, CP intensity scores, and EMA ratings are listed in Table 2. The groups did not differ significantly on any of these variables.

EMA Scores Descriptive Analyses

The overall means for the EMA questions across assessment times are given in Table 3. Fig 3 shows the mean daily ratings for 3 variables (overall pain, emotional distress, and fatigue) over the 30-day assessment period. Patients' reports on these variables were relatively stable

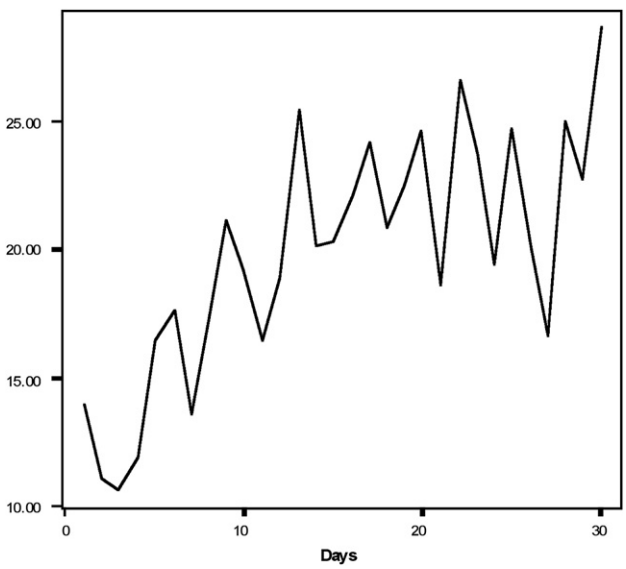

Figure 2. Daily missing response rate across 30 days.

Table 2. Mean TP Parameters and EMA Ratings for the Patients With More Than 30% Missing Response Rate and Those Whose Missing Response Was Less Than 30%

Variables	>30% Missing (N = 18)	<30% Missing (N = 63)
TP counts	17.00 (1.41)	16.56 (1.74)
TP intensity	3.99 (1.74)	4.19 (1.60)
CP intensity	1.15 (1.45)	1.06 (1.00)
EMA Pain	2.56 (.97)	2.76 (.83)
EMA Fatigue	3.47 (.87)	3.53 (.83)
EMA Emotional Distress	2.11 (1.22)	2.19 (1.07)

over time but differed from day to day and assessment epoch to assessment epoch.

Descriptive and Cross-Sectional Correlational Results for Pain, Fatigue, and Emotional Distress

In order to evaluate the presence of diurnal variation of the main FMS-related symptoms, we calculated the mean values of the 3 variables of interest by daily epoch (see Table 4). Clinically, many FMS patients often report some daily patterns of their symptoms; for example, fatigue may often may be more severe towards the end of the day,[35] whereas many patients report worse pain in the morning. However, our results showed that the mean values were quite consistent across epochs. There were no significant variations.

Overall, the variables were moderately correlated with one another cross-sectionally (Table 5). Epoch-by-epoch analyses also show the same patterns. Little variation is observed in the strength of the relationships among the variables by epoch.

Sequential Relationships Among Pain, Fatigue, and Emotional Distress

We conducted a series of mixed-effects analyses to examine the variation in scores for pain, fatigue, and emotional distress from epoch to epoch as well as from day to day, in order to identify possible sequential associations among these factors. In the models, the estimated fixed effects represent the average proportion change in the outcome measure predicted by a unit change in the predictor variable. Table 6 presents all significant estimated fixed and random effects of predictor variables for current pain, fatigue, and emotional distress.

Table 3. Mean Values for EMA Items Across 30 Days (the Items Were Rated on a 0 to 6 Point Scale Except for the Number of Hours Slept in the Previous Night)

EMA Items	Means	SD
Overall pain	2.73	1.28
Fatigue	3.53	1.43
Head pain	2.01	1.48
Emotional distress	2.13	1.62
Abdominal pain	1.24	1.32
Relaxed	3.11	1.43
Muscle pain	2.99	1.31
Swelling	1.24	1.40
Hours slept in the previous night	7.12	1.62
Quality of sleep	3.12	1.40

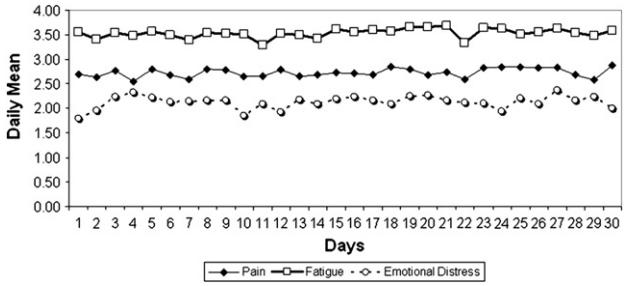

Figure 3. Daily mean pain, fatigue, and emotional distress rating across 30 days.

Not surprisingly, there were significant autoregressive relationships for each variable (see Table 6). That is, pain was best predicted by prior pain, and the same relationship was observed for fatigue and emotional distress. The question of interest, however, was whether variation in 1 symptom could be uniquely predicted by either of the other 2 symptoms from the past epoch (ie, X-1 Epoch) or past day (ie, X-1 Day) controlled for all other predictors in the relevant past. Controlled in this manner of the relevant past, unit increases in (X-1 Epoch) pain and (X-1 Epoch) emotional distress predicted 9% ($P < .001$) and 7% ($P < .001$) increases, respectively, in current fatigue ($P < .001$). Controlled for the relevant past, a unit increase in (X-1 Epoch) pain predicted a 7% ($P < .001$) increase in current emotional distress, but no unique predictive effect emerged for fatigue. Controlled for the relevant past, a unit increase in (X-1 Epoch) fatigue and (X-1 Day) fatigue predicted a 7% ($P < .001$) and 3% ($P < .001$) increases, respectively, in current pain ($P < .001$) whereas no unique predictive effect emerged for emotional distress. The bottom of Table 6 presents the residual contemporaneous correlations, controlled for the relevant past. These small-to-moderate correlations summarize covarying associations that cannot be causally resolved.

Random Effects

In these models, the effects of the predictor variables are unique for each patient. The standard deviations in Table 6 indicate the typical deviation of a patient's unique predictor effect from the population average.

Table 4. Mean Values of Pain, Fatigue, and Emotional Distress by Daily Epoch Over 30 Days

	Epoch		
Variables	Morning	Afternoon	Evening
Pain	2.70 (1.30)	2.69 (1.27)	2.79 (1.28)
Fatigue	3.50 (1.49)	3.45 (1.40)	3.65 (1.38)
Emotional distress	2.07 (1.61)	2.17 (1.64)	2.15 (1.62)

Table 5. Cross-Sectional Relationships* Among Pain, Fatigue, and Emotional Distress: Overall, and by Daily Epoch

	Pain	Fatigue	Emotional Distress
Overall			
Pain		.47**	.34**
Fatigue			39**
Morning Epochs			
Pain		.47**	.34**
Fatigue			.39**
Afternoon Epochs			
Pain		.49**	.32**
Fatigue			.40**
Evening Epochs			
Pain		.46**	.36**
Fatigue			.39**

*Typical within-day correlations obtained as maximum-likelihood estimates of covariance matrix scaled by standard deviations and assumed invariant over days.
**$P < .001$

Significant deviations were found for yesterday's (X-1 Day) pain as a predictor of current pain (SD = .08) and emotional distress (SD = .10). Individuals also differed significantly for previous (X-1 Epoch) fatigue effects on current fatigue (SD=.07) and previous (X-1 Epoch) emotion on current emotion (SD = .15).

Typical deviations in an individual's overall level from the population average are given by intercept standard deviations. These systematic differences were moderately large and highly significant for all 3 outcome variables. Typical deviations for single assessments from an individual's unique predicted values are given by the error standard deviations. Error SDs were large and highly significant for all 3 outcome variables.

To illustrate the nature of the sequential relationships between predictor and outcome variables, Fig 4 shows the association between yesterday's (X-1 Day) pain on current emotional distress for 2 participants. For the sake of simplicity, the figures show the daily average scores but the analyses were based upon (X-1 Day) values. Participant #2038 had a relatively strong association between yesterday's pain and current emotional distress (R^2 = .223). Increased pain on Day 22 **(A)** was followed by increased emotional distress on Day 23 **(A')**, while decreased pain on Day 23 **(B)** was followed by decreased emotional distress on Day 24 **(B')**. The associations found for Participant #2060 illustrate the small but significant individual differences found. Participant #2060 had a strong association between yesterday's pain on emotional distress (R^2 = .216), but in the opposite direction from what was predicted. For this individual, an increase in pain on Day 12 **(A)** was followed by decreased emotional distress on Day 13 **(A')**, and decreased pain on Day 13 **(B)** was followed by increased emotional distress on Day 14 **(B')**.

The significant controlled associations found between some predictor and outcome variables indicate that some causal relationships may pertain. Collectively, these results suggest an asymmetry in which emotional distress and pain Granger-cause increased fatigue; fatigue, but not emotional distress, Granger-causes increased pain;

Table 6. Relationship of Current Pain, Fatigue, and Emotion Ratings With Ratings Given at the Previous Time Period and at the Same Time Period on the Previous Day for the Group, and Individual Differences Within Associations

	*Estimated Fixed Effects** *(Population Average Effects) of Predictor Variables on Outcome Variables*			*Estimated Random Effects†* *(Individual Variation) About Population Average Effects: Standard Deviations*		
Predictor Variable	*Current Pain*	*Current Fatigue*	*Current Emotion*	*Current Pain*	*Current Fatigue*	*Current Emotion*
Previous pain	.266‡	.092‡	.069‡	§	§	§
Yesterday's pain	.142‡	§	§	.081¶	§	.100¶
Previous fatigue	.069‡	.169‡	§	§	.074¶	§
Yesterday's fatigue	.029¶	.159‡	§	§	§	§
Previous emotion	§	.069‡	.276‡	§	§	.148‡
Yesterday's emotion	§	§	.101‡	§	§	§
Intercept				.386‡	.366‡	.524‡
Error				.927‡	1.122‡	1.132‡
					Residual Correlation#	
Current fatigue				.338‡		
Current emotion				.220‡	.250‡	

*Expected change in the population average for an outcome variable given a 1-unit change in a predictor variable, when controlling for all other predictor variables.
†Typical deviations in a patient's unique predictor effect from the population average, shown as a standard deviation.
‡Significant at $P < .001$.
§Not significant.
¶Significant at $P < .05$.
#Residual contemporaneous correlation, assumed invariant across days and epochs.

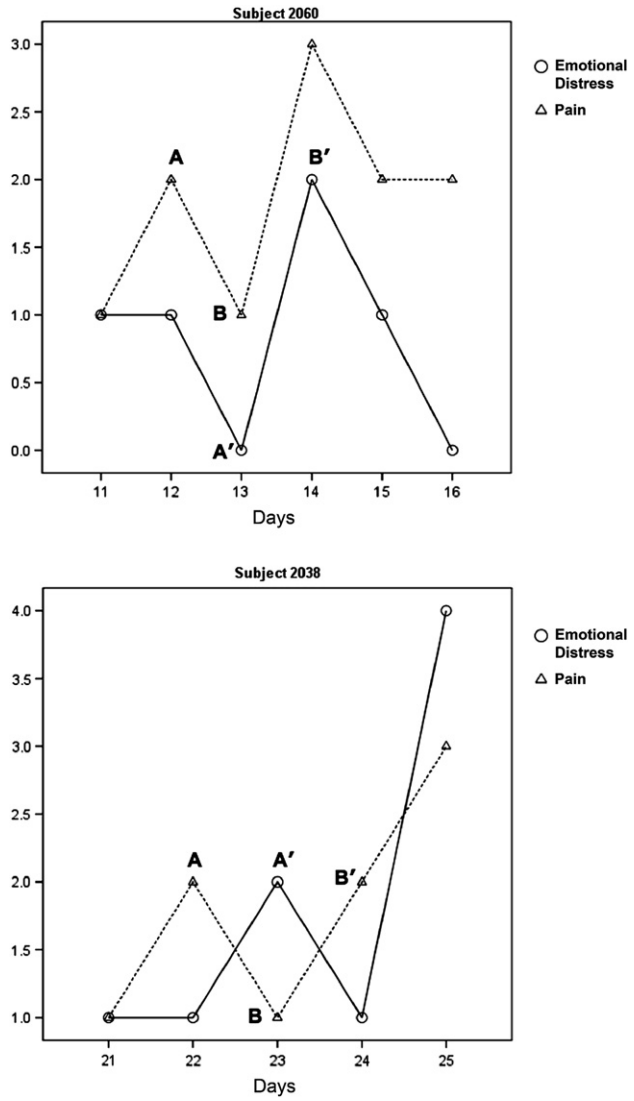

Figure 4. Individual differences in the sequential association of pain and emotional distress.

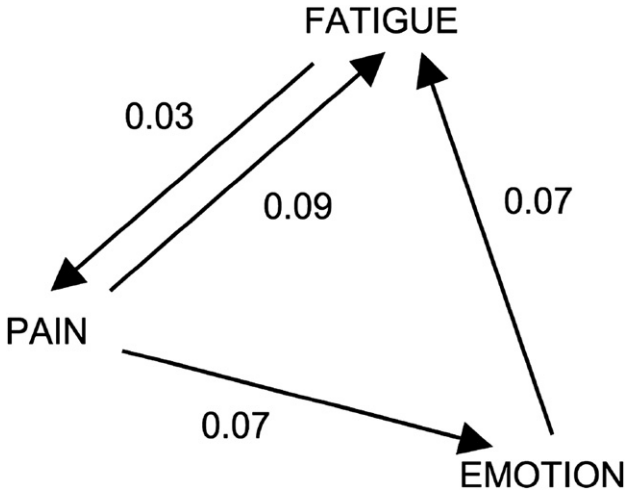

Figure 5. Granger causality for pain, fatigue, and emotional distress.

and pain, but not fatigue, Granger-causes increased emotional distress (Fig 5). These causal associations shown were significant but quite small, and vary significantly from person to person.

Discussion

The overall response rate for EMA data acquisition was 80.5% with approximately 1/3 of the patients having less than 10% missing responses and 1/3 having 10 to 20% missing responses over the 30-day assessment. Not surprisingly, there was a significant trend to increasing numbers of missing responses with increasing duration. The frequency of missing responses appeared to increase markedly following the first week of the assessment. Response rates seem comparable to 1 published report on EMA assessment over time.[13] The results suggest that the optimal period for using the EMA assessment method may be 1 week.

The central symptoms of FMS—pain, fatigue, and mood—seem to maintain a stable course over time in terms of overall level. Nevertheless, there is considerable variation from 1 epoch to the next and from day-to-day, with prior observations on the same and different variables explaining some of the change. When they change, the direction of change seems consistently positive; a unit increase in symptoms of pain, fatigue, or emotional distress during the immediately preceding epoch (X-1 Epoch) or during the same epoch the previous day (X-1 Day) predicted an increase in the same symptoms in question. Our results support the temporal relationship within the same variables (ie, pain-pain over time), although the strength of the relationship seems to lessen with longer duration between the 2 assessment time points. A unit increase in previous pain predicted 26% increase for pain; that is, if previous pain increased by 1, then the current pain would be increased by .26. An example may clarify the results. If a person's pain intensity increased up by 1 unit from 4 to 5 in the previous epoch, the person's pain would increase to 5.26. Previous emotion predicted a 28% increase for emotional distress. Fatigue had a slightly smaller, though still significant and positive, association, with a 17% rise predicted by a unit increase in previous fatigue.

Of perhaps more interest was the finding of Granger-causal relationships among pain, fatigue, and emotional distress. When controlling for effects of prior observations on the same symptom, the results show some interesting asymmetrical relationships among these symptoms. Previous pain was a significant predictor of both fatigue and emotional distress such that if a patient had worsening of pain in the previous epoch, they were more likely to experience increased fatigue and emotional distress. Thus, a 1.0-point increase in pain in the previous epoch would predict a .09 increase in current fatigue and a .07 increase in emotional distress. Likewise, prior worsening of fatigue predicted current increased pain, and previous increase in emotional distress predicted current fatigue. All but one intersymptom Granger-causal relationship was demonstrated with the 1-epoch timeframe. The exception was the previous worsening of fatigue predicting current increase in pain. The effect was small (3%; that is, a 1-unit increase

in fatigue at the immediately previous epoch would predict a .03-unit increase in pain in this epoch) but statistically significant.

The failure of emotional distress to predict subsequent pain may seem counterintuitive. Clinical anecdotes often indicate that both patients and clinicians view psychological distress to be a significant contributor for the exacerbation of pain in FMS. Interestingly, however, the literature is quite equivocal on this matter. Mood disturbance has been shown to be associated with sensitivity to experimentally induced noxious stimuli[14,32] and TP sensitivity.[43] Modest correlation between depressive mood and clinical pain has been reported in some studies,[5,19,23] but not others.[7,28] In the present study, we employed a large number of longitudinal, repeated multivariate observations yet failed to demonstrate the Granger-causal predictive value of emotional distress for pain. There may be several possible explanations for our findings.

First, emotional distress might be a transient state and not an enduring trait. In other words, perhaps it fluctuates with circumstances to a greater extent than pain or fatigue. The current analysis does not support this interpretation, however. Although the autoregressive relationships for emotional distress are somewhat lower than those for pain and fatigue, stable individual differences (as indexed by the intercept standard deviation) are actually greater for emotional distress than for pain or fatigue. In other words, emotional distress seems less likely to fluctuate within a person, and is more likely to be constant across circumstances than are pain and fatigue.

Nonetheless, emotional distress, pain, and fatigue do co-occur systematically (see the bottom of Table 6), though, in ways that cannot be causally disentangled using the Granger logic. Recent research suggests that the effect of antidepressants on pain in FMS appears to be relatively independent of its effect on mood.[3] However, past research has shown that a significant level of depressive symptoms compromises patients' ability to effectively cope with chronic pain[39] and is a risk factor for subsequent development of chronic pain.[9,22] A pathological level of distressed mood is always a serious health concern that contributes to the chronicity of pain and disability.[30,41] In future research, sequential analyses evaluating the effect of specific depressive symptoms on pain severity may further our understanding of this issue.

Because the causal associations among symptoms of FMS identified in this study were small and varied from person to person, no definitive conclusions can be drawn. Nevertheless, this study has shown that analyzing multiple measures of multiple symptoms longitudinally can be helpful in clarifying relationships among the multiple symptoms that have heretofore seemed too complicated to disentangle. Understanding the temporal interrelationship among different symptoms is important for understanding multisymptom syndromes such as FMS. Patients frequently report that having 1 symptom leads to a cascade of problems. Identifying how change in 1 symptom affects other symptoms when they are so closely related is a challenging task; identifying the causal priority in a syndrome with multiple symptoms is difficult. However, if we have a reasonable idea of which symptoms are likely to adversely impact others, this may lead to the development of more efficient treatment plans that have some prophylactic value. Our results suggest possible treatment strategies. If fatigue affects pain, then applying a treatment designed to reduce fatigue could trigger a beneficial cascade and contribute to overall pain reduction, and pain reduction can then propagate further to improve both fatigue and emotional distress. Our findings, though limited, also suggest that treatment of emotional distress may have secondary benefits for fatigue, but may not lead to reduced pain. Since these symptoms vary in an ensemble that would unlikely be completely separated, reducing any symptom is necessarily beneficial to the overall distress the patient experiences at any given time.

EMA has some advantages over traditional self-report assessment methods. Typical in-clinic and laboratory assessment methods require patients' ability to accurately recall symptoms over a period of time in an unfamiliar place where they are removed from the contexts in which the symptoms actually occur. One alternative method is to use a paper-and-pencil form of symptom diary at specified times. This method has the advantage of allowing researchers to obtain multiple symptom ratings across time in the home environment. Furthermore, it does not depend on recall, summarizing symptom severity from the past. However, the paper-and-pencil diary method has limited control over when and how the form is completed. Indeed, research has shown compliance with paper diaries tends to be suboptimal.[20,36,38]

EMA, unlike paper-and-pencil methods, monitors compliance and does not allow responders to "cheat." Carrying and using small electronic devices such as cell phones and personal desktop assistants has become much more common in recent years. Thus, use of such devices for EMA over a period of 1 week does not present an imposition to most patients. This approach allows assessment of patients' symptoms in real-time without requiring recall, and to do so in their natural environment, thus significantly improving the validity of the data. However, EMA is not entirely problem free. Questions need to be simple and the number of assessment items must be limited. The items to be included in EMA should be well justified in the overall conceptualization of the problem that is being tested. Although EMA has potential uses in research, the applicability, given the costs and complexities in hardware, software, and user interface in the clinic, remains to be demonstrated.[40]

Overall, the results from the present study support the utility of EMA in assessing FMS symptoms over an extended period with a reasonable level of missing data, particularly within 1 week. The results from the temporal analyses of pain, fatigue, and emotional distress suggests that the prior levels of the symptoms of interest—both an epoch before and a day before—are the best predictors of current symptom severity; however, other parameters seem to make small but significant contributions to

the current level of symptom burden. Future research needs to address the clinical significance of these contributions and how such temporal relations can be used to delineate and optimize treatment options.

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